Lopinavir/Ritonavir (LPV/r, Kaletra)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric oral solution: 80 mg/20 mg LPV/r/mL (contains 42.4% alcohol by volume)

Pediatric Tablets: 100 mg/25 mg LPV/r

Tablets: 200 mg/50 mg LPV/r

Dosing Recommendations

Neonate dose (age <14 days):
No data on appropriate dose or safety of LPV/r in this age group. Do not administer to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.

Infant dose (age 14 days–12 months) in individuals not receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (NFV):
Once-daily dosing is **not** recommended.

The recommended dose of the oral solution is 300 mg/75 mg LPV/r per m^2 of body surface area twice daily or 16 mg/4 mg LPV/r per kg of body weight twice daily.

NOTE: Use of 300 mg/75 mg LPV/r per m^2 of body surface area in infants 12 months of age or younger is associated with lower LPV trough levels than those found in adults; in infants, LPV dosing should be adjusted for growth at frequent intervals (see Pediatric Use).

Pediatric dose (age >12 months–18 years) in individuals not receiving concomitant NVP, EFV, FPV, or NFV:
Once-daily dosing is **not** recommended.

Body surface area dosing:
230 mg/57.5 mg LPV/r/m^2 of body surface area per dose twice daily in antiretroviral (ARV)-naive patients older than age 1 year. For patients already receiving LPV/r, immediate dose reduction at age 12 months is not recommended: many practitioners would allow the patient to "grow into" the 230 mg/m^2 dosage as they gain weight over time (see Pediatric Use).

300 mg/75 mg LPV/r/m^2 of body surface area per dose twice daily is used by many clinicians, espe-

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, taste alteration
- Asthenia
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding in patients with hemophilia
- PR interval prolongation
- QT interval prolongation and torsade de pointes
- Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see *Major Toxicities*).

Special Instructions

- LPV/r tablets can be administered without regard to food, but recognize that administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. Do not crush or split tablets.
- LPV/r oral solution should be administered with food. A high-fat meal increases absorption, especially of the liquid preparation.
- The poor palatability of LPV/r oral solution can sometimes be partially masked with flavorings or foods (see *Pediatric Use*).
- LPV/r oral solution can be kept at room temperature up to 77°F (25°C) if used within 2 months. If kept refrigerated (2° to 8°C or 36°

cially for patients previously treated with ARV drugs (see Pediatric Use).

Weight-based dosing:
<15 kg: 12 mg/3 mg LPV/r per kg of body weight per dose twice daily.

≥15 kg to 40 kg: 10 mg/2.5 mg LPV/r per kg of body weight per dose twice daily.

≥40 kg: 400 mg/100 mg LPV/r per dose twice daily.

Weight Band Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children/Adolescents Without Concomitant NVP, EFV, FPV, or NFV.

Body Weight (kg)	Body Surface Area (m^2)	Recommended Number of 100 mg/25 mg LPV/r Tablets Given Twice Daily
15 to 25 kg	≥0.6 to <0.9 m^2	2
>25 to 35 kg	≥0.9 to <1.4 m^2	3
>35 kg	≥1.4 m^2	4 (or two 200 mg/50 mg LPV/r adult tablets)

Pediatric dose (age >12 months to 18 years)
For individuals receiving concomitant NVP, EFV, FPV, or NFV.
(These drugs induce LPV metabolism and reduce LPV plasma levels; increased LPV/r dosing is required with concomitant administration of these drugs and/or in treatment-experienced patients in whom reduced susceptibility to LPV is suspected, such as patients with prior treatment with other protease inhibitors [PIs].)

Do not administer LPV/r with NVP, EFV, FPV, or NFV in infants 6 months of age or younger.

Once-daily dosing is **not** recommended.

Body surface area dosing:
300 mg/75 mg LPV/r/ per m^2 of body surface area per dose twice daily.

Weight-based dosing:
<15 kg: 13 mg/3.25 mg LPV/r per kg of body weight per dose twice daily.

to 46°F) LPV/r oral solution remains stable until the expiration date printed on the label.

- LPV resistance-associated substitutions: LPV/r can be administered once daily (800 mg/200 mg) in adults with fewer than three LPV resistance-associated substitutions. Once-daily administration of LPV/r is not recommended for adult patients with three or more of the following LPV resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

Metabolism

- Cytochrome P 450 3A4 (CYP3A4) inhibitor and substrate.
- **Dosing of LPV/r in patients with hepatic impairment:** LPV/r is primarily metabolized by the liver. Caution should be used when administering LPV to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the coformulation of LPV/r, the RTV acts as a pharmacokinetic (PK) enhancer, not as an ARV agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

≥*15 kg to 45 kg:* 11 mg/2.75 mg LPV/r per kg of body weight per dose twice daily.

≥*45 kg:* Use adult dose twice daily.

Weight Band Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children With Concomitant NVP, EFV, FPV, or NFV

Body Weight (kg)	Body Surface Area (m^2)	Recommended Number of 100 mg/25 mg LPV/r Tablets Given Twice Daily
15 to 20 kg	≥0.6 to <0.8 m^2	2
>20 to 30 kg	≥0.8 to <1.2 m^2	3
>30 to 45 kg	≥1.2 to <1.7 m^2	4 (or two 200 mg/50 mg LPV/r tablets)
>45 kg	≥1.7 m^2	4 or 6 (or two 200 mg/50 mg LPV/r adult tablets)*

**The higher dose may be considered in treatment-experienced patients when decreased sensitivity to LPV is suspected because of clinical history or documented by resistance testing.*

NOTE: In children, use of 230 mg/57.5 mg LPV/r per m^2 of body surface area (when not coadministered with NVP, EFV, FPV, or NFV) or use of 300 mg/75 mg LPV/r per m^2 of body surface area (when coadministered with NVP, EFV, FPV, or NFV) is associated with area under the curve (AUC) LPV levels similar to AUC achieved with standard doses in adults, but it is associated with lower trough levels in children than in adults. Therefore, some clinicians may choose to initiate therapy with higher doses of LPV/r when coadministered with these drugs or in PI-experienced pediatric patients who may have reduced PI susceptibility (see Pediatric Use).

Adult dose(age >18 years):
In patients with fewer than three LPV-associated mutations (see Special Instructions for list):

800 mg/200 mg LPV/r once daily; **or**

400 mg/100 mg LPV/r twice daily.

Do **not** use once-daily dosing in children or adolescents. Once-daily dosing should not be used in

patients receiving concomitant therapy with NVP, EFV, FPV, or NFV.

In patients with three or more LPV-associated mutations (see Special Instructions for list):

400 mg/100 mg LPV/r twice daily.

In patients receiving concomitant NVP, EFV, FPV, or NFV):
Food and Drug Administration (FDA)-approved dose is 500 mg/125 mg LPV/r twice daily, given as a combination of two tablets of 200/50 mg LPV/r and one tablet of 100 mg/25 mg LPV/r. Most Panel members would use 600 mg/150 mg LPV/r for ease of dosing. Once-daily dosing should **not** be used.

LPV/r in combination with saquinavir (SQV) hard-gel capsules (Invirase) or in combination with maraviroc (MVC):
SQV and MVC doses may need modification. See sections on SQV or MVC.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Metabolism:* Lopinavir/ritonavir is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Before lopinavir/ritonavir is administered, the patient's medication profile should be carefully reviewed for potential drug interactions with lopinavir/ritonavir. Fluticasone, a commonly used inhaled and intranasal steroid, should not be used in patients treated with lopinavir/ritonavir.

Major Toxicities:

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, and hyperlipidemia, especially hypertriglyceridemia.
- *Less common (more severe):* Lipodystrophy.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life threatening in rare cases). PR interval prolongation. QT interval prolongation and torsade de pointes may occur. Lopinavir/ritonavir should not be used in the immediate postnatal period in premature infants because an increased risk of toxicity in premature infants has been reported. These toxicities in premature infants include transient symptomatic adrenal insufficiency[1]; life-threatening bradyarrhthymias and cardiac dysfunction[2-3, 4]; and lactic acidosis, acute renal failure, central nervous system (CNS) depression, and respiratory depression[4]. These toxicities may be from the drug itself and/or from the inactive ingredients in the oral solution, including propylene glycol 15.3%, and ethanol 42.4%[4]. Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with lopinavir/ritonavir[1].

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/LPV.html).

Pediatric Use:
Lopinavir/ritonavir is FDA approved for use in children. Ritonavir acts as a PK enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

There is some controversy about the dosing of lopinavir/ritonavir in children. Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The "directly scaled" dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 m^2. For the adult dose of 400/100 mg lopinavir/ritonavir, the appropriate pediatric dose would be approximately 230/57.5 mg lopinavir/ritonavir per m^2. However, younger children have enhanced lopinavir clearance and need higher drug doses to achieve drug exposures similar to those in adults treated with standard doses. To achieve similar C_{trough} to that observed in adults, the pediatric dose needs to be increased 30% over the dose that is directly scaled for body surface area.

For 12 children 6 months to 12 years of age receiving 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), the mean C_{trough} was 4.74 ± 2.93 mcg/mL (about 67% of the adult value of 7.1 ± 2.9 mcg/mL)[5]. For 15 children 6 months to 12 years of age treated with 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), the mean C_{trough} was 7.91 ± 4.52 mcg/mL, similar to that in adults treated with 400 mg/100 mg lopinavir/ritonavir twice daily[5]. Therefore, the Panel recommends using 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area in infants up to 12 months of age; in addition, some clinicians may choose to initiate therapy in children 12 months to 12 years of age using 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (when given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the drug label-recommended 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily[6].

The PK behavior of the oral solution at approximately 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily was evaluated in infants younger than 6 weeks of age[7] and infants 6 weeks to 6 months of age[8]. PK values found in these studies are compared to those in older children[5] and adults[9] in the table below. Values are means; all data shown performed in the absence of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

	Adults[9]	Children[5]	Children[5]	Infants at 12 months[10]	Infants 6 weeks–6 months[8]	Infants <6 weeks[7]
N	19	12	15	20	18	9
Dose LPV	400 mg	230 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2
AUC mcg*hr/mL	92.6	72.6	116	101	74.5	43.4
C_{max} mcg/mL	9.8	8.2	12.5	12.1	9.4	5.2
C_{trough} mcg/mL	7.1	4.7	7.9	4.3	2.7	2.5
C_{min} mcg/mL	5.5	3.4	6.5	3.8	2.0	1.4

Even at this higher dose, predose (C_{trough}) levels were highly variable but were lower in infants than in children older than age 6 months and were lowest in the youngest infants 6 weeks of age or younger compared

with those between ages 6 weeks and 6 months. By age 12 months, lopinavir AUC was similar to that found in older children[10]. Because infants gain weight rapidly in the first months of life, one important way to optimize lopinavir dosing is to weigh the patient and adjust the dose for growth at frequent intervals. Given the safety of doses as high as 400 mg/m^2 body surface area in older children and adolescents[11], some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg/m^2 body surface area dose to let the infant "grow into" the 300 mg/m^2 body surface area amount.

For children, as in adults, the lopinavir C_{trough} is further reduced by concurrent treatment with NNRTIs or concomitant fosamprenavir or nelfinavir and, as in adults, higher doses of lopinavir are recommended if the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus nevirapine, the mean lopinavir C_{trough} was 3.77 ± 3.57 mcg/mL[5]. For 12 children treated with 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily, the mean C_{trough} was 5.62 ± 3.32 mcg/mL. Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of lopinavir/ritonavir, but the variability in concentration is much higher in children than adults[5-6]. In a study of 15 children with HIV infection treated with the combination of lopinavir/ritonavir using an increased dose of 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus efavirenz 14 mg/kg of body weight per dose once daily, the median 12-hour lopinavir trough was 5.7 mcg/mL, but there was 34-fold interindividual variation in lopinavir trough concentrations, and 5 of 15 (33%) children had lopinavir 12-hour trough concentrations less than 1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV[12]. A PK study in 20 children 10 to 16 years of age treated with the combination of lopinavir/ritonavir 300 mg/75 mg per m^2 of body surface area twice daily plus efavirenz 350 mg/m^2 of body surface area once daily showed adequacy of the lopinavir trough values[13].

Once-daily dosing of lopinavir/ritonavir 800 mg/200 mg administered as a single daily dose is FDA approved for treatment of HIV infection in therapy-naive adults older than age 18 years. However, once-daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM) because of high interindividual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus in 21 of 59 patients (35.6%)[14-17]. Compared with the soft-gel formulation of lopinavir/ritonavir, the tablet formulation has lower variability in trough levels[17-18], but the Panel remains concerned about the long-term effectiveness of once-daily lopinavir/ritonavir in children.

Lopinavir/ritonavir has been shown to be effective as salvage therapy in children with HIV and severe immune suppression[19-20], although patients with greater prior exposure to ARVs may have slower reductions in virus load to undetectable concentrations[20-21] and less robust response in CD4 percentage[22]. Twice-daily doses of lopinavir used in this cohort were 230 to 300 mg/m^2 of body surface area in 39% of patients, 300 to 400 mg/m^2 of body surface area in 35%, and greater than 400 mg/m^2 of body surface area per dose in 4%[22].

More important than viral resistance to lopinavir is the relationship of the drug exposure (trough plasma concentration measured just prior to a dose, or C_{trough}) to the susceptibility of the HIV-1 isolate (EC50). The ratio of C_{trough} to EC50 is called the inhibitory quotient (IQ), and in both adults and children treated with lopinavir/ritonavir, virus load reduction is more closely associated with IQ than with either the C_{trough} or EC50 alone[23-26]. A study of the practical application of the IQ to guide therapy using higher doses of lopinavir/ritonavir in children and adolescents showed the safety and tolerability of doses of 400 mg/100 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine or efavirenz) and 480 mg/120 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (with nevirapine or efavirenz)[11]. Results of a modeling study suggest that standard doses of lopinavir/ri-

tonavir are likely to be inadequate for treatment-experienced children and underscore the potential utility of TDM in children previously treated with PIs and now on salvage therapy with lopinavir/ritonavir[27].

Lopinavir/ritonavir tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed, and result in significantly reduced AUC, C_{max}, and C_{trough} compared with taking the whole tablet. The variability of the reduced exposure with the crushed tablets (5% to 75% reduction in AUC) means that a dose modification cannot be relied on to overcome the reduced absorption. Crushed tablets cannot be recommended for use[28]. In a PK study in Thailand, 21 of 54 children used cut (not crushed) pills with no negative impact on PK measurements[18].

Compared with children treated with NNRTI-based regimens, those treated with lopinavir/ritonavir may have less robust weight gain and smaller increases in CD4%[29-30]. The poor weight gain associated with lopinavir/ritonavir is of uncertain cause.

The poor palatability of the oral solution can be a significant challenge to medication adherence for some children and families. Administration of the medication before or after ice chips, sweet or tangy foods, chocolate syrup, or peanut butter, for example, or with flavorings added to it by a pharmacy may partially improve taste.

References

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